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Cortical dopamine D_2/D_3 receptors are a common site of action for antipsychotic drugs – an original patient data meta-analysis of the SPECT and PET in vivo receptor imaging literature

Running title: Meta analysis of cortical and striatal D_2/D_3 occupancy by antipsychotic drugs

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Abstract

Subject numbers in neuroreceptor imaging studies of antipsychotic treatment in schizophrenia are generally insufficient to directly test the relationship of regional D_2/D_3 and $5HT_{2A}$ receptor binding to clinical efficacy. We selected positron emission tomography (PET) and single photon emission computed tomography (SPECT) studies of antipsychotic dose vs. occupancy at both temporal cortex and striatal D_2/D_3 receptors. We selected corresponding SPECT and PET studies of $5HT_{2A}$ receptor occupancy. We also selected randomized double blind clinical trials of antipsychotics, where patients were treated with randomly assigned fixed doses. For each antipsychotic drug, we compared the optimum effective antipsychotic dose with the dose inducing maximal occupancy of D_2/D_3 receptors in striatum, and in temporal cortex as well as at $5HT_{2A}$ receptors. Both first- and second-generation antipsychotic drugs (FGA, SGA) produced high temporal cortex D_2/D_3 occupancy. Only FGA produced high striatal D_2/D_3 receptor occupancy. The clinically effective dose showed correlation with doses inducing maximal dopamine D_2/D_3 receptor occupancy both in striatum and in temporal cortex, the strongest correlation being with temporal cortex binding. EPSE were primarily related to striatal D_2/D_3 receptor occupancy. There was no correlation between $5HT_{2A}$ occupancy and clinically effective dose. We conclude that cortical dopamine D_2/D_3 receptor occupancy is involved in antipsychotic efficacy, with striatal D_2/D_3 occupancy having a likely therapeutic role whilst also inducing EPSE. We found no evidence for $5HT_{2A}$ blockade involvement in antipsychotic action, although we cannot exclude this possibility.

Key words: Schizophrenia, antipsychotic, efficacy, limbic selectivity, EPSE, SPECT

Introduction

Cortical dopamine D_2 receptors have been hypothesized to be a common site of action for both first-generation (typical) antipsychotics (FGAs) and second-generation (atypical) antipsychotics (SGAs).[1] The antagonism of $5HT_{2a}$ receptors has also been hypothesized to play a critical component in SGA therapeutic action.[2] Positron Emission Tomography (PET) and Single Photon Emission Computed Tomography (SPECT) allow the *in vivo* imaging of regional antipsychotic medication binding to receptor subtypes to explore the relationship of receptor binding to efficacy and side effects in living schizophrenic patients. These studies are low throughput, high cost and are highly labour intensive. Consequently sample sizes are usually too small to permit extensive analyses of receptor occupancy versus drug efficacy.

Seeman and Snyder noted a striking correlation between the dose of an antipsychotic to produce D_2 receptor occupancy in rodent brain tissue and the clinically effective dose.[3, 4] We decided to use a similar method, pooling original patient data from multiple centres (total n=139), and comparing the clinically effective dose for different antipsychotic drugs, with the dose required for each drug to induce maximal occupancy at dopamine receptors in striatum and temporal cortex, as well as in $5HT_{2a}$ receptors. Through this approach, we have been able to explore the role of D_2/D_3 binding in striatum and temporal cortex plus $5HT_{2a}$ binding on clinical efficacy.

Methods

Identification and selection of regional dose:occupancy studies

Medline and PubMed were searched to identify all PET or SPECT studies examining dopamine and/or serotonin receptor occupancy of FGAs and SGAs, using the keywords "antipsychotic", "occupancy", "dopamine", "serotonin" and "emission tomography". We selected studies in which D_2/D_3 receptor availability was estimated in the same patient in both

striatum and temporal cortex, and in which patients were in steady state on an antipsychotic drug (chronic dosing). These criteria were designed to minimize any variation in apparent receptor occupancy due to differences in ligand affinity for receptor subtypes, inter-subject variability of receptor expression and differences in drug dose.

One hundred and thirty nine studies were identified using our Medline search strategy. In total, 15 papers met our inclusion criteria for estimation of regional D_2/D_3 receptor occupancy with antipsychotic dose [5-19] and 3 papers met our inclusion criteria to analyze the relationship between antipsychotic dose and $5HT_{2a}$ receptor occupancy.[20-22] Of the papers that were excluded, 78 papers reported striatal dopamine receptor occupancy only, 20 were review articles without detailed data. The remaining papers were excluded because they did not involve SPECT or PET radioligands, they were non-human studies, or they did not study D_2/D_3 or $5HT_{2a}$ receptors.

Consistency of imaging studies

The methodology of all the selected imaging studies was broadly comparable, although there were two distinct designs of study to measure dopamine D_2/D_3 receptor binding with either simultaneous measurement of striatal and extrastriatal antipsychotic binding (single ligand studies) or measurement of striatal and extrastriatal antipsychotic binding in each subject with different tracers on separate occasions (dual ligand studies).

In brief, patients with schizophrenia on a steady dose of antipsychotic medication and healthy age and sex-matched controls were recruited after informed consent was obtained. A radiolabelled ligand specific for the dopamine D_2/D_3 receptor ([^{123}I]epidepride, [^{18}F]fallypride or [^{76}Br]FLB-457 for single ligand studies or [^{11}C]raclopride for striatal and [^{11}C]FLB-457 for temporal D_2 receptor binding in dual-ligand studies) or $5HT_{2a}$ receptor ([^{18}F]setoperone) was

injected. Images were acquired sequentially after injection (on 2 separate occasions for the dual-ligand studies). Occupancy by the antipsychotic drug was estimated by comparison of receptor binding in drug treated patients with controls or unmedicated patients (after adequate washout time).

Approximately 2/3 of the patients from the dopamine receptor occupancy studies were imaged using [^{123}I]epidepride,[11, 10, 5, 16, 13] whilst the rest were imaged using [^{18}F]fallypride, [^{76}Br]FLB-457 or [^{11}C]raclopride and [^{11}C]FLB-457 PET.[6-9, 14, 15, 17-19] Almost all the patients (n=70) from the $5HT_{2a}$ receptor occupancy studies were imaged with [^{18}F]setoperone,[22, 21] while 5 patients were imaged using [^{11}C] N-methylspiperone.[20] Table 1 shows the ligand used, the number of subjects in each study, and the method of receptor quantification for the dopamine receptor occupancy studies.

Data extraction – imaging studies

For each subject from the dopamine imaging studies, we extracted antipsychotic drug taken; dose of antipsychotic drug; estimated occupancy at striatal dopamine D_2/D_3 receptors; and estimated occupancy at temporal D_2/D_3 receptors, contacting the authors where necessary for additional data. From these data, we determined dose vs. occupancy on a per subject basis. We also calculated mean D_2/D_3 occupancy at striatum and temporal cortex for each drug. In one study,[8] we were unable to match antipsychotic doses in a given subject with D_2/D_3 receptor occupancy data for the same subject, and so we could use data from this study to calculate mean occupancies only.

For the serotonin imaging studies, we extracted estimated mean occupancy of $5HT_{2a}$ receptors at fixed doses of each antipsychotic drug. For striatal and temporal cortex D_2/D_3 receptor occupancy and for $5HT_{2a}$ occupancy, we calculated the dose at which consistent maximal

occupancy occurred (ED95occ). As FGAs consistently showed significantly higher D_2/D_3 receptor occupancy in striatum at doses imaged compared to SGAs (which had a mean striatal occupancy of 49%), it is possible that the ED95occ for FGAs (calculated from the doses imaged) may have meant that like was not being compared with like with respect to striatal D_2/D_3 receptor occupancy. Therefore, we also calculated the dose at which FGAs would be expected to achieve 49% striatal D_2/D_3 receptor occupancy. We used the slope of the significant linear correlation between FGA dose given to each individual patient, in haloperidol equivalents, and their individual striatal occupancy to estimate the dose necessary to achieve a mean striatal occupancy of 49% for FGAs.

Identification and selection of dose:efficacy and dose:side-effect studies

In order to calculate the dose-response curve for efficacy and extrapyramidal side effects (EPSE), we selected studies in which patients with schizophrenia were randomly assigned to placebo and to fixed doses (or dose ranges – at steady state) of second-generation antipsychotics and efficacy and EPSE assessed by double-blind techniques and included all such trials. The design is necessary for a valid assessment of dose response.

For olanzapine we included two studies that performed dose ranging of acute patients: one assigning patients to placebo and a narrowly defined dose range of 5±2.5, 10±2.5, and 15±2.5 mg/day of olanzapine,[23] and the other assigning patients to placebo, 1mg and 10 mg/day of olanzapine.[24] For risperidone, we used two large registrational studies, one from the United States [25] and one from Canada comparing patients to placebo 2, 4, 8, and 16 mg/day.[26] For quetiapine, we used three fixed dose studies: One assigning patients to placebo, 75, 150, 300, 450, and 600 mg/day quetiapine,[27] the second assigning patients to placebo, low dose range (< 250 mg/day), and high dose range (>250mg/day) quetiapine,[28] and the third assigning patients to 400, 600 and 800 mg/day quetiapine.[28] For sertindole, we used two studies: One comparing

placebo to, 8, 12, and 20 mg/day sertindole and 4, 8, and 16 mg/day haloperidol,[29] and another comparing sertindole to placebo, 8, 12, and 20 mg/day.[30] For amisulpride, there was only one dose:response study that compared 100, 400, 800 and 1200 mg/day amisulpride, with no placebo group.[31] Adjustment for the placebo effect in this study was made by extrapolating the placebo effect from other studies. For clozapine, there was again only one dose:response study comparing 100, 300 and 600mg/day.[32] There was no placebo group, but during the washout phase, placebo treated patients deteriorated, so we used baseline period for an estimate of placebo response.

Using higher doses than necessary can produce an increase in side effects but no greater increase in therapeutic benefit because the dose-response curve is sigmoidal. We calculated the optimal dose from the dose-response curve from the large random-assignment double-blind fixed-dose clinical trials. We termed this the ED95 clinically effective dose (ED95eff), since it corresponded to the dose at which the drug is maximally effective for almost all the patients. The methodology of study identification, analysis, and for calculating dose-response has been previously described and more details about such calculations are reported in detail in our previous publication.[33]

Analyses

Comparison of regional receptor occupancy in different antipsychotic drugs

We compared mean D_2/D_3 receptor occupancy in striatum, temporal cortex or their ratio in FGA versus SGA using unpaired student's t-test with unequal variances.

Relationship of Clinical Response to receptor occupancy

We plotted the log of ED95eff (y-axis) against the log of ED95occ for D_2/D_3 receptor occupancy in the temporal cortex. As FGAs did not show comparable striatal D_2/D_3 receptor

occupancies to SGAs at doses imaged (discussed above), we plotted both the dose inducing maximal striatal D_2/D_3 receptor occupancy by FGAs, as well as the estimated FGA dose to achieve the same striatal occupancy as seen with SGAs (49%). We compared the correlations of efficacy vs. striatal or temporal cortex with a t-test for the difference between two correlations sharing a common variable [34].

As the $5HT_{2A}$ receptor occupancy studies did not always include doses equivalent to the ED95 efficacy (therapeutic doses), there were three dimensions to examine: the dose used to image, the level of $5HT_{2A}$ occupancy at this dose, and the ED95eff (therapeutic dose). We plotted the range of doses imaged vs. $5HT_{2A}$ occupancy with a line, and indicated the ED95eff for each drug using a separate marker.

We examined the relationship between ED95occ for and ED95eff for 5HT2A occupancy and for striatal and temporal cortex D_2/D_3 receptor occupancy using Pearson's product-moment correlation.

Sensitivity Analysis

Although our estimates of ED95eff were based on the evidence derived from the dose finding studies of each compound, there remained some uncertainty about the most effective clinical dose for some agents, e.g., the two dose-response studies of quetiapine yielded slightly different estimates, and opinion differs about the optimal dose of clozapine. In order to address these issues, we performed sensitivity analyses at 28 different doses (approximately four on each of the seven drugs) and correlated these to receptor occupancy.

Relationship of EPSE to receptor occupancy

We explored the EPSE risk of FGAs by correlating the doses (in haloperidol equivalents) in

the individual patients from the imaging studies with striatal and temporal receptor occupancy.

Comparison of results using different ligands and different modeling methods

SPECT and PET studies of occupancy can be divided into those using a single ligand to estimate binding in both striatal and cortical brain regions ([^{123}I]epidepride, [^{18}F]fallypride) and those using different ligands for each brain region ([^{11}C]raclopride for striatum and [^{11}C]FLB-457 for cortical brain regions). Analysis of binding is now usually estimated using the simplified reference tissue model (SRTM). Some earlier studies employed a simpler (ratio) method (see table 1). There has been some concern that different methods of measuring dopamine receptor occupancy may be affected by different imaging methods, or different methods of quantification of the radiotracer binding.[35, 17, 36-38] In order to address these concerns, we included all studies using different methods of analysis in the meta-analysis. We also analysed the differences in receptor occupancy reported by both single ligand and two ligand methods of imaging separately and then separately analysed the differences between the SRTM and ratio methods of binding estimation.

To study the difference between the single- and the dual-ligand approach to determine occupancy, we used an ANOVA with drug (typical-atypical) and single versus dual-ligand as independent factors, and D_2/D_3 receptor occupancy of striatal or temporal cortex as the dependent variable without the interaction in the final model. A similar ANOVA was done using drug and SRTM versus ratio method and an ANCOVA with single versus dual-ligand and SRTM versus ratio methods as covariants, to adjust the typical-atypical differences.

Results

First- and second-generation antipsychotic drugs and D_2/D_3 occupancy

FGAs (n=28) produced significantly higher striatal (74+/-SD=12%) occupancy than SGAs (n=115, 49+/-21%; t = 8.8,df=73.7,p< $4*10^{-13}$). Both FGAs and SGAs produced 70-80% D_2/D_3 occupancy in the temporal cortex, though FGAs had slightly higher cortical occupancy (77+/-12%) than SGAs (67+/-19%)(unpaired t-test, t=3.5,df=62.3,p=0.001) (Figure 1A).

FGAs showed a significantly greater occupancy of striatal dopamine D_2/D_3 receptors (S/T ratio = 96%, SD=24%) than SGAs (S/T ratio = 74%, SD=35%; t=3.7,df=41,p<0.001). All SGAs showed greater differentiation between cortical and striatal D_2/D_3 binding within each subject than FGAs (amisulpride 36+/-15%; clozapine 17+/-16%; olanzapine 40+/-16 %; quetiapine 20+/-12; risperidone 26+/-7%; sertindole 16+/-10%, FGAs 5+/-17%).

Correlation of clinically effective dose with receptor occupancy

There was a high correlation of ED95eff with temporal cortex dopamine D_2/D_3 receptor ED95occ (r=0.95, n=7, p<0.001; see Figure 1B). A less strong correlation was also found between ED95eff and actual striatal dopamine D_2/D_3 receptor ED95occ (r=0.76, n=7, p=0.046; see Figure 1C; significance of difference between r=0.95 and r=0.76: t=1.7, DF=4, p= .08). Substituting the FGA ED95occ with the dose required to achieve the same striatal occupancy as SGAs had no significant effect on the correlation (r=0.76, n=7, p=0.046). Interestingly, the correlation between the natural log of the antipsychotic doses was highly significant for both striatum and temporal cortex D_2/D_3 ED95occ vs. ED95eff, although temporal cortex still showed a slightly higher correlation (temporal cortex r=0.99, n=7, p<0.0001; striatum high FGA occupancy r=0.94, n=7, p<0.005; striatum same FGA occupancy as SGA r=0.86, n=7, p<0.05; significance of difference between r=0.99 and r=0.86: t=3.1,df=4, p=.02). The correlation between ED95eff and $5HT_{2a}$ receptor ED95occ was not statistically significant (r=0.29, n=5, ns), partly because amisulpride produced no $5HT_2$ blockade, but also because clozapine led to very high $5HT_{2A}$ receptor occupancy at sub-

therapeutic doses (see figure 1D).

Sensitivity analysis

The mean correlation (r) between ED95eff and temporal or the actual striatal D_2/D_3 receptor occupancy using 28 different dose schedules was r=0.98 for temporal cortex and r=0.69 for striatum. Thus the sensitivity analyses were consistent with the primary analysis.

Antipsychotic propensity for EPSE and regional dopamine receptor occupancy:

Doses of FGAs were moderate. Of the 28 subjects, 18 received haloperidol with an average dose of 9 mg/day, while most others received high potency FGAs. Only three subjects received doses of haloperidol over 12 mg/day. The FGA dose (in haloperidol equivalents) for each individual was significantly correlated with striatal D_2/D_3 receptor occupancy (r=0.59, df=22, p=0.004; p=0.004), but for temporal cortex D_2/D_3 receptor occupancy, this correlation was not significant (r=0.38, df=22, p=ns).

Comparison of results using SRTM vs. ratio modeling

The mean temporal cortex D_2/D_3 occupancy estimated was 61% by the ratio method and 78% with SRTM, a difference of 14.6% (95% CI: to 21, F=21.3, F=8.8: df=1,127: p=0,004). However the ratio and SRTM methods did not produce a significant alternation in striatal occupancy. (F = 1.5, df=1,127: ns). Importantly the SRTM or ratio method did not alter the difference between typical versus atypical occupancy. The interaction of the SRTM/Ratio method and typical/atypical drug was essentially zero for both striatal (F = 0.0, df=1,127:ns) and temporal cortex (F= 0.1,df=1,127:ns).

Comparison of results using single vs. dual ligands

The ANOVA showed a significant difference between the single- and the dual-ligand method used in both brain areas (striatal and temporal). The single-ligand studies reported 18% (95% CI: 10% to 25%) *lower* striatal D_2/D_3 receptor binding than the dual-ligand studies (F = 22; df = 1,128; p =0.000007). In the temporal cortex the single-ligand studies found 13% (95% CI: 6% to 21%) *higher* D_2/D_3 receptor occupancy than the dual-ligand studies (F=13; df = 1,128; p=0.0006). The interaction of FGA-SGA used with single- versus dual-ligand method was not significant for striatal (F=1.5; df=1,128; NS) or temporal cortex (F=0.7; df=1,128; NS).

After adjustment by ANCOVA with single/dual ligand and SRTM/ratio as covariate, the striatal occupancy was 74% (95% CI: 66% to 82%) for typical antipsychotics, and 47% for atypicals (95% CI: 44% to 54%), a difference of 27% (18% to 36%), and statistically significant (F= 37, df=1, 127, p= 0.00000005).

Discussion

This is the first meta-analysis pooling original patient PET and SPECT receptor imaging data to better understand the mode of action of antipsychotic drugs in vivo in patients with schizophrenia. We found that both SGAs and FGAs produce high (70-80%) D_2/D_3 occupancy in the temporal cortex, but that only the FGAs produce high D_2/D_3 receptor occupancy in the striatum. The clinically effective dose (ED95eff) showed a highly significant linear correlation with the dose required to induce maximal temporal cortex D_2/D_3 receptor occupancy. There was a less strong, but still significant, linear correlation with the dose required to induce maximal striatal dopamine D_2/D_3 receptor occupancy, whether actual doses imaged, or estimated FGA dose required to produce the same striatal occupancy as SGAs were used. This suggests that the temporal cortex and striatum are both possible targets for antipsychotic efficacy.

We found that the dose of FGA was linearly related to striatal occupancy, and not to temporal cortical occupancy. As propensity to induce EPSE increases with increasing FGA dose, this suggests that EPSE are more closely related to dopamine receptor occupancy in striatum than in temporal cortex.

The absence of a significant correlation between efficacy and $5HT_{2a}$ binding, and the fact that atypicality is possible without significant $5HT_{2A}$ binding (amisulpride), suggests that $5HT_{2a}$ binding is not a central component of either the therapeutic or EPSE components of SGA antipsychotic action, although we cannot completely exclude the possibility that $5HT_{2A}$ blockade is important in the functionality of some antipsychotic drugs, since high $5HT_{2A}$ receptor occupancy at doses used therapeutically is a feature of 4 out of the 5 SGAs investigated in this study.

Methodological consideration

Assumptions about drug mechanisms

In grouping drugs together (SGA vs. FGA) we have made the assumption that these drugs behave similarly to others in the same group. This is not necessarily the case since both FGAs and SGAs have widely varying action at other receptor subtypes besides dopamine D_2 receptors. It should be noted that the FGAs imaged were either haloperidol or other high potency antipsychotic drugs. If lower potency FGAs had been imaged, it is possible that the difference between FGAs and SGAs in terms of striatal and cortical D_2 receptor occupancy would not have been so marked.

Dose:efficacy and Dose:occupancy estimation

The ideal method of estimating the relationship of clinical efficacy and side effect profile to

receptor occupancy is to assess dose-response curves and imaging in the same patient. In order to achieve this, it would be necessary to evaluate large samples of patients who are in an episode of acute psychotic illness at baseline, and then again for 3-6 weeks treatment with different antipsychotic drugs. Patients should also be randomly assigned to multiple fixed doses on the log-linear part of the dose-response curve. Three such studies have yielded important results, but they examined striatal D_2/D_3 receptor occupancy only.[39-41] We feel that such designs have considerable advantages in that they allow the assessment of dose-response for efficacy and extrapyramidal side effects and measurement of receptor occupancy in the same subject.

Since data employing antipsychotic dosing and simultaneous striatal and extrastriatal D_2/D_3 receptor imaging in the same patient were not available, we used data from well-designed clinical trials for determination of ED95 for clinical efficacy and EPSE in order to combine with the ED95 receptor occupancy results from the SPECT and PET imaging studies. Patients in the dosing studies were therefore not the same who underwent scanning. It is possible that the doses leading to 95% clinical effect and EPSE could differ somewhat between the populations of the dosing studies and the scanning studies, which would lead to a degree of inaccuracy in the correlation of clinical effect and EPSE with dopamine receptor occupancy. As the patients in the dosing studies were similar to those in the scanning studies, in that they were chronic patients with schizophrenia on long-term antipsychotic treatment, we believe that this effect should be minimal. Sensitivity analysis shows that the correlation of D_2/D_3 occupancy and clinical dose was consistent over a wide choice of clinical doses.

Scanning and modeling methods

In keeping with previous reports, we found that single-ligand studies tended to report lower striatal occupancy regardless of modeling method used, and that dual-ligand studies

(employing [^{11}C]FLB-457) reported lower temporal cortex occupancy. One possible reason for this is given by the suggestion that [^{11}C]FLB-457 might not reach equilibrium within the maximum scan time possible with an [^{11}C] labeled tracer.[35] [^{11}C]FLB-457 has also been shown to have significant binding to D_2 receptors in the cerebellum and, as this region is used as a reference region in SRTM analysis (assumed to have no significant binding), measures of cortical D_2 receptor occupancy might be significantly underestimated using this ligand.[38] On the other hand, the use of a single high affinity ligand to estimate binding in both striatum and temporal cortex might underestimate striatal occupancy.[36]

We found a difference between single- and dual-ligand methods, but no interaction between method and drug administered, indicating that the difference in receptor occupancy of typical and atypical drugs occurs with both methods to an approximately equal degree. We also found that method of analysis (ratio vs. SRTM) made no significant difference to the results.

It should be noted that interpretation of drug binding studies using PET and SPECT imaging is complex, since changes in ligand binding can be affected by the affinity of the ligand, the affinity of the drug and the level of endogenous dopamine in different brain regions.[42] Whether the higher temporal cortex binding by SGAs detected by the single-ligand method is actually a true increase in receptor occupancy by antipsychotic drug, or alternatively, a complex interaction between the affinity state of the D_2/D_3 receptor, endogenous dopamine, antipsychotic drug affinity and ligand affinity for the receptor is currently not clear. It is possible that the finding of regional preferential occupancy of antipsychotic drugs is an artefact of the imaging method used. However, the fact remains that PET or SPECT studies employing a single ligand are able to distinguish between high potency FGAs and SGAs based on the ratio between striatal and temporal occupancy.

Plotting occupancy vs. clinical dose

In striatum, FGAs had high occupancy at all doses imaged, whereas SGAs had a lower D_2 receptor occupancy over all doses. This posed some difficulty in plotting 95% D_2 receptor occupancy for SGAs, but since occupancy was stable over the dose ranges imaged, we assumed that the imaged occupancy value was the maximum obtainable in the striatum by SGAs, and calculated ED95 occupancy on this basis. It is possible that the lower correlation between striatal D_2 receptor occupancy and clinically effective dose may have been driven by this difference between SGAs and FGAs. When the dose of typical to produce the same occupancy is plotted, the relationship is clearly non-linear. This, however, is a projected dose from the individual patient data. We caution the reader to keep this in mind.

Cortical dopamine receptor binding

It has long been suspected that mesolimbic dopamine circuits may be of more relevance to the symptoms of schizophrenia than the nigrostriatal pathway,[43, 44] and structural and functional changes in hippocampus and temporal cortex have been some of the most robust findings in the illness.[45-47] Other brain regions have been implicated in schizophrenia however, particularly dorsolateral prefrontal cortex, anterior cingulate and thalamus,[48-50] and it is likely that pathological changes in schizophrenia affect multiple cortical and subcortical brain regions. The results from the present meta-analysis support the hypothesis that cortical D_2/D_3 receptors are likely to be an important site of antipsychotic action,[1] but this does not exclude the involvement of other brain regions that have not been studied.

One small but well designed study included in this paper found a significant relationship between striatal D_2 receptor binding and reduction in psychotic symptoms, but found a less strong correlation with D_2 binding in cortical brain regions.[19] The less strong correlation may have arisen because dopamine receptor density in temporal cortex is low relative to striatum

and so extrastriatal measurements tend to have lower signal to noise ratio than striatal measurements, requiring greater numbers to find a significant correlation. It should be noted that we also found a correlation between antipsychotic efficacy and striatal D_2/D_3 receptor occupancy and so cannot exclude the involvement of striatal D_2/D_3 receptor blockade in antipsychotic action.

Sub-striatal regions

It is possible that, in addition to inducing extrapyramidal side effects, dopamine receptor occupancy in striatum may have therapeutic effects. This might arise through action at sub-regions of the striatum. The striatum is split into three functionally distinct units, which blend into different anatomical regions. The putamen is primarily sensori-motor in function, the caudate performs more cognitive and associative roles, while the ventral parts of the striatum are involved in emotional processing, salience and reward.[51, 52] Blockade of dopamine receptors in caudate and ventral striatum might, therefore, be expected to also be involved in antipsychotic efficacy and so D_2/D_3 receptor binding in these striatal sub-regions would be expected to correlate with antipsychotic efficacy. Two pharmacologically distinct SGAs (amisulpride and risperidone) both show selective occupancy of D_2/D_3 receptors in the head of caudate over the putamen,[53] suggesting that reduced D_2/D_3 receptor binding in the putamen alone may be the distinguishing feature of atypical antipsychotic drugs.

As very few of the papers included in this meta-analysis examined subregions of the striatum, it is possible that the correlation between antipsychotic efficacy and striatal occupancy may have been driven through dopamine receptor occupancy in caudate or ventral striatum. New developments in SPECT and PET resolution, allowing greater distinction between nigrostriatal, mesolimbic and mesocortical striatal regions, will help to further elucidate the importance of sub-regional binding of antipsychotic drugs for efficacy and side-effect profile.

Conclusions

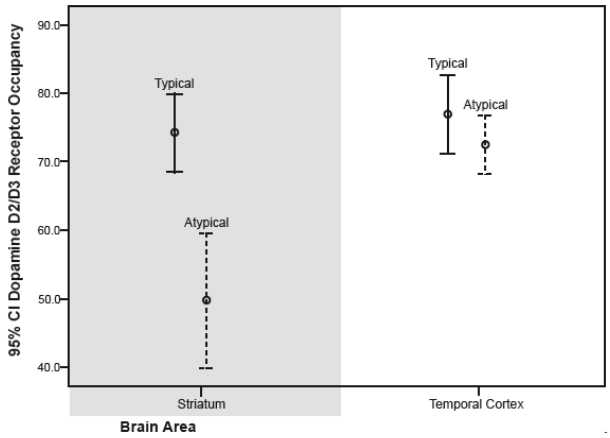
This novel meta-analysis of original patient data provides the first human *in vivo* evidence that the clinically efficacious dose of antipsychotic drugs is related to dopamine D_2/D_3 receptor occupancy in cortical brain regions. D_2/D_3 binding in sub-regions of the striatum is also likely to be therapeutically important. The data suggest that extrapyramidal side effects are primarily related to striatal, and not cortical, D_2/D_3 occupancy. $5HT_{2A}$ occupancy does not appear to be a central component of SGA efficacy or EPSE profile.

Table 1: **Papers included in meta-analysis. Antipsychotic, ligand and analysis method used (ratio or SRTM – simple reference tissue model) are displayed. Number of subjects in each study (n) are shown. * Data from 3 extra previously unpublished subjects on clozapine from Pilowsky et al. 2007 were included. 5 subjects in Bigliani et al. 1999 overlapped with Pilowsky et al. 2007 and were not included twice. 5 subjects from Xiberas et al 2002a overlapped with Xiberas et al 2002b, and were not included twice, and one further subject from Xiberas et al 2002a had almost undetectable plasma blood levels and 0% dopamine receptor occupancy, and was not included in the analysis. Although included for the group comparison of FGA vs. SGA occupancy, subjects from Kessler et al. 2005 were not used for the within subject analysis of striatal vs. temporal cortex occupancy as individual dose:occupancy data were not available.**

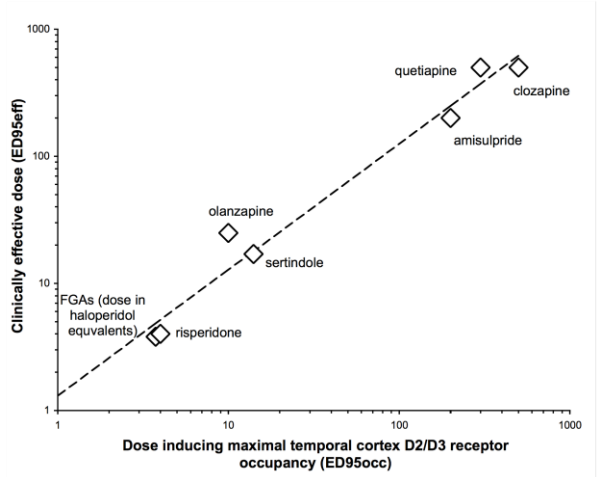
Paper	Drug	Ligand	Analysis Method	n
Pilowsky et al. 1997	Clozapine	[^{123}I]epidepride	ratio (equilibrium)	7 *
	FGAs			5
Farde et al. 1997	Clozapine	[^{11}C]raclopride/[^{11}C]FLB-457	ratio (curve integral)	1
	FGAs			3
Bigliani et al. 1999	FGAs	[^{123}I]epidepride	ratio (equilibrium)	12 *
Bigliani et al. 2000	Olanzapine			5
	Sertraline			4
Stephenson et al. 2000	Quetiapine			6
Talvik et al. 2001	Clozapine	[^{11}C]raclopride/[^{11}C]FLB-457	SRTM	4
	FGAs			3
Xiberas et al. 2001a	Amisulpride	[^{76}Br]FLB-457	ratio (equilibrium)	10*
Xiberas et al. 2001b	FGAs			4
	Risperidone			3
	Clozapine			3
	Amisulpride			5
	Olanzapine			4
Nyberg et al. 2002	Sertindole	[^{11}C]raclopride/[^{11}C]FLB-457	ratio (curve integral)	4
Bressan et al. 2003a	Amisulpride	[^{123}I]epidepride	SRTM	6
Bressan et al. 2003b	Risperidone			8
Grunder et al. 2005	Clozapine	[^{18}F]fallypride	SRTM	15 *
Kessler et al. 2005	Olanzapine			6 *
	FGAs			6 *
Agid et al. 2006	Risperidone	[^{11}C]raclopride/[^{11}C]FLB-457	SRTM	5
	Olanzapine			9
Kessler et al. 2006	Clozapine	[^{18}F]fallypride	SRTM	6
	Quetiapine			7

Figure 1 A: dopamine D_2/D_3 receptor occupancy (error bars=SD) by FGAs (n=28) and SGAs (n=111) in striatum and temporal cortex. FGAs (n=28) produced significantly higher striatal (74+/-SD=12%) occupancy than SGAs (n=115, 49+/-19%; t = 8.8,df=73.7, $p< 4*10^{-13}$). **B:** Correlation of ED95 clinically effective dose vs. ED95 temporal cortex D_2/D_3 receptor occupancy by antipsychotic drugs ($p<0.001$). **C:** Correlation of ED95 clinically effective dose vs. ED95 striatal D_2/D_3 receptor occupancy by antipsychotic drugs ($p<0.05$). **D:** Plot of $5HT_{2A}$ ED95 clinically effective dose (diamond), ED95occ (cross) and doses actually imaged in each subject indicated as a broken line showing the upper to lower range vs. $5HT_{2a}$ receptor occupancy (%) by antipsychotic drugs.

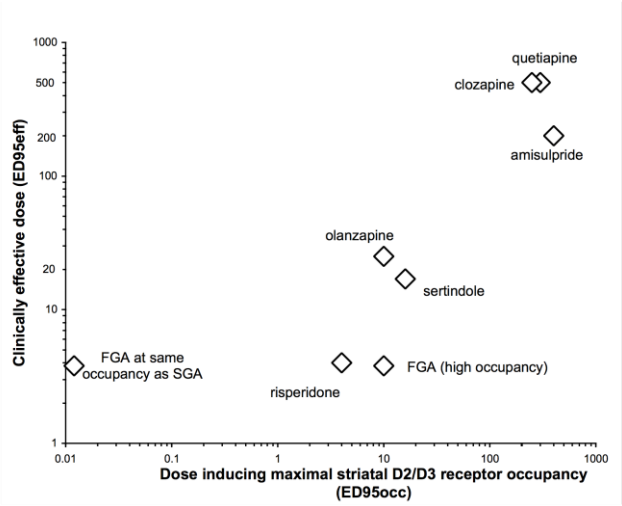
A



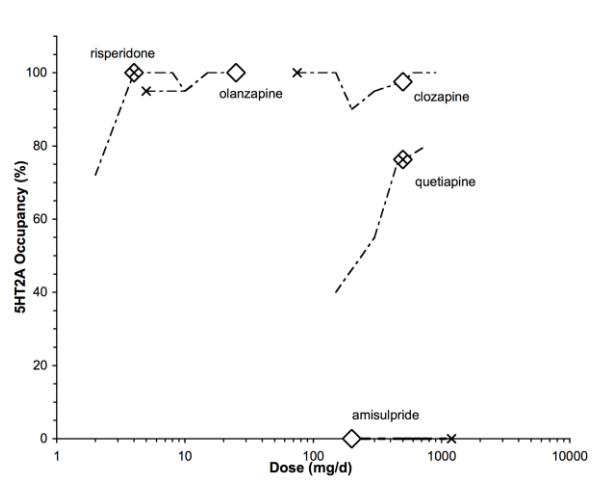
B



C



D



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